

Amendments to the Claims:

Please amend the claims to read as follows:

1 - 18. (Cancelled)

19. (Currently amended) An Uncaria extract composition made according to a method comprising the steps of:

- a) preparing a polar solvent extract of *Uncaria* plant matter, where the polar solvent extraction is selected from one of the extraction methods from the group of extraction methods consisting of extraction with water, extraction with a water solution of a polar alcohol, extraction with a water solution of acetonitrile and extraction with a water solution of a polar organic solvent, and running the extract through a first column that comprises hydroxy group containing resin, resin having hydrophobic characteristics but without any hydroxy groups, or a mixture of both;
- b) eluting the first column with distilled water, followed by eluting with not more than 2-4 column bed volume washings with a dilute polar alcohol/water solution having an alcohol/water ratio not greater than 50/50, and discarding any eluate;
- c) eluting the first column with one or more column bed volume washings of a polar alcohol/water solution having an alcohol/water ratio between 50/50 and substantially pure alcohol, and collecting and drying the eluted volumes to a dried material.

20. (Cancelled)

21. (Currently amended) The composition of according to claims 39, 43, 44, 47 ~~and or~~ 48, wherein the fraction is fraction H.

22. (Cancelled)

23. (Currently amended) An Uncaria extract composition made according to a method comprising the steps of:

- a) preparing a polar solvent extract of *Uncaria* plant matter, where the polar solvent extraction is selected from one of the extraction methods from the group of extraction methods consisting of extraction with water, extraction with a water solution of a polar alcohol, extraction with a water solution of acetonitrile and extraction with a water solution of a polar organic solvent,

and running the extract through a first column that comprises hydroxy group containing resin, resin having hydrophobic characteristics but without any hydroxy groups, or a mixture of both;

b) eluting the first column with distilled water, followed by eluting with not more than 2-4 column bed volume washings with a dilute polar alcohol/water solution having an alcohol/water ratio not greater than 50/50, and discarding any eluate;

c) eluting the first column with one or more column bed volume washings of a polar alcohol/water solution having an alcohol/water ratio between 50/50 and substantially pure alcohol, and collecting and drying the eluted volumes to a dried material;

d) applying an aqueous solution of the dried material to a second column, eluting the material from the column with successive column volumes of water/methanol mixtures containing 0.1% TFA, beginning with 25% methanol and increasing to 100% methanol in 25% increments, and collecting, combining and drying the fractions to a dried material; and

e) making one or more injections of a solution of the dried material of step (d) above in a solvent comprising water/methanol 80/20 containing about 0.1% TFA and applied at about 150 mg/run to a preparative HPLC Dynamax 5 $\mu$  C-18 column with dimensions of about 21.4mm X 25cm, with detection at 280 and 300 nm, the gradient conditions being 0 to 3 min for 20% to 25% B gradient, 3 to 9 min for 25 to 45% B gradient, all at a flow rate of about 20 ml/min, and collecting a fraction eluting between 7-8 minutes from start of elution.

24. (Currently amended) A method of treatment or management of an amyloidosis, or a disease related to alpha-synuclein, in a mammalian subject ~~susceptible to, or afflicted by, the amyloidosis or alpha-synuclein disease~~ in need thereof, the method comprising the step of administering to the subject a therapeutic amount of the composition of claim 23.

25. (Currently amended) A method of treatment or management of an amyloidosis, or a disease related to alpha-synuclein, in a mammalian subject ~~susceptible to, or afflicted by, the amyloidosis or alpha-synuclein disease~~ in need thereof, the method comprising the step of administering to the subject a therapeutic amount of an Uncaria extract composition comprising fraction G, fraction H, fraction I, fraction K<sub>1</sub>, fraction K<sub>2</sub>, fraction L, fraction M, fraction N and/or fraction O of claims 39, 43, 44, 47 and 48.

26. (Cancelled)
27. (Currently amended) The method of claims 24, ~~25 or 26~~ wherein the amyloidosis is associated with Alzheimer's disease.
28. (Cancelled)
29. (Currently amended) A method for the treatment, inhibition or management of amyloid fibril or alpha-synuclein fibril formation, deposition, accumulation, aggregation and/or persistence in a mammalian subject in need thereof, the method comprising the step of administering to the subject a therapeutic amount of the composition of claims 19 or any one of the fractions of claims 23 and 39 to 49.
30. (Currently amended) The method of claim 29, wherein the route of administration of the method of treatment is selected from the group consisting of oral administration, parenteral injection, intraperitoneal injection, intravenous injection, subcutaneous injection, or aerosol spray administration.
31. (Currently amended) A pharmaceutical composition comprising a therapeutically effective amount of the composition of claim 19, or a therapeutically effective amount of any one of the fractions of claims 23, and 39 to 49, ~~the therapeutic~~ wherein the therapeutically effective amount of the composition or fractions ~~selected for efficacy in~~ is effective for treating an amyloid disease in a patient.
32. (Cancelled)
33. (Currently amended) The pharmaceutical composition of claim 31, wherein the therapeutically effective amount of the composition or fractions comprises a dosage in the range of from about 10 to 1,000 mg/kg of body weight of the patient.
34. (Currently amended) The pharmaceutical composition of claim 33, wherein the therapeutically effective amount of the composition or fractions comprises a dosage in the range of from about 10 to 100 mg/kg of body weight of the patient.
35. (Cancelled)
36. (Currently Amended) The pharmaceutical composition of claims 31 ~~or 35~~, wherein said amyloid disease for treatment is Alzheimer's disease.

37. (Currently Amended) The pharmaceutical composition of claims 31 ~~and 33 to 36~~, further comprising a pharmaceutically acceptable carrier, diluent, or excipient.

38. (Previously presented) The pharmacological composition of claims 31 and 33 to 37, wherein the therapeutically effective amount of the composition or fractions has an amyloid inhibitory activity or efficacy greater than 50%.

39. (Currently amended) An *Uncaria* extract composition made according to a method comprising the steps of:

- a) adding 4000ml of methanol to 1 kg of *Uncaria tomentosa* and mixing
- b) centrifuging the mixture at X2,500g using a centrifuge for 30 minutes and collecting the supernatant;
- c) extracting the insoluble material about 3 more times as steps a and b above;
- d) combining the supernatants and evaporating to dryness (or until about 500 ml volume is reached) using a rotary evaporator at 50°C,
- e) taking the powdered extract (or about 500ml volume), washing 4 times with 300ml of petroleum ether, and discarding the ether layer,
- f) evaporating the methanol to dryness using a rotary evaporator at 50°C;
- g) extracting the solid material 5 times with 150ml of distilled water, followed by centrifugation at 2,500Xg for 30 minutes each time;
- h) combining the supernatants and then lyophilizing using a freeze-dryer;
- i) dissolving the resulting lyophilized extract into about 500 ml of distilled water, and applying 50-100ml portions to a 400 ml LH-20 column equilibrated with distilled water.
- j) eluting the LH-20 column with 1,100ml of distilled water (~3 column volumes) and discarding the amber/yellow, non-active fractions;
- k) eluting the LH-20 column with 1,100ml of 100% methanol (~3 column volumes) and collecting a set of active fractions and evaporating to dryness using a rotary evaporator at 50°C;
- l) dissolving the fractions of step k in water (80mg/ml) and applying 5 ml at a time to a 10gm disposable C18 SPE column equilibrated in solvent A (solvent A is 95% water/5% acetonitrile/0.1% TFA);

m) washing the column with 3 volumes of solvent A and discarding the eluate;

n) eluting the column with 3 volumes of solvent A containing 12.5% solvent B (solvent B is 95% acetonitrile/5% water/0.1% TFA) and lyophilizing the eluate;

o) taking 50mg of the lyophilized eluate of step (n) and injecting multiple times into a Hewlett-Packard 1100 Series HPLC instrument with diode array detector, fitted with a 2.2cm X 25 cm Vydac 218TP1022 C18 reverse-phase column maintained at 25°C and at a flow rate of 5 ml/min;

p) eluting the sample with the following solvent profile, 10% B for 0 to 20 minutes, 10 -100 % B gradient for minutes 20 to 30, and 100-10% B gradient for minutes 30-31, where B is 95% acetonitrile/5% water/0.1% TFA;

q) and separating and collecting the fractions G (13-14 minutes), ~~fraction~~-H (17-20 minutes), ~~fraction~~-I (21 minutes), ~~fraction~~-K<sub>1</sub> (24 minutes), ~~fraction~~-K<sub>2</sub> (25 minutes), ~~fraction~~-L (26-27 minutes), ~~fraction~~-M (27-28 minutes), and ~~fraction~~-N (28-29 minutes), whereby the *Uncaria* extract composition comprises one or more fractions.

40. (Currently amended) The composition of claim 19, wherein; an aqueous solution of the dried material from step (c) is applied to a second column comprising a hydrophobic resin, the second column having been preparatorily equilibrated in a solvent comprising about 95% water/5% acetonitrile, referred to herein as solvent A; eluting the second column with more solvent A and discarding the eluate; and eluting the second column with a mixture of solvent A containing 10-15% of a solvent comprising about 95% acetonitrile/5% water, referred to herein as solvent B, and collecting and drying the eluted volumes to a dried material.

41. (Currently amended) The composition of claim 19, wherein; an aqueous solution of the dried material from step (c) is applied to a second column comprising a hydrophobic resin, the second column having been preparatorily equilibrated in a solvent comprising about 95% water/5% acetonitrile, referred to herein as solvent A, eluting the second column with more solvent A and discarding the eluate; and eluting the second column with a mixture of solvent A containing 10-15% of a solvent comprising about 95% acetonitrile/5% water, referred to herein as solvent B, and collecting and drying the eluted volumes to a dried material, and a solution of the dried material in a solvent selected from the group of solvents consisting of water, water/dilute alcohol and solvent

A, and no more than 10% of solvent B, is injected into an HPLC instrument having a diode array uv/vis detector with a graphic display, the HPLC instrument further comprising a reverse-phase column; and eluting the material through the HPLC column using a solvent gradient profile as follows: 10% solvent B for about the first 20 minutes from start of elution, 10 to 100% solvent B gradient for about minutes 20 to 30 from start of elution, and 100 to 10% solvent B gradient for about minutes 30 to 32 from start of elution, while observing the uv/vis detector graphic display during the elution gradient over time, and separating fractions of the eluate at elution times corresponding to times associated with the graphic display peaks.

42. (Currently amended) The composition of claim 19, wherein; a solution of the dried material of step (c) in a solvent selected from the group of solvents consisting of water, water/dilute alcohol and a solvent comprising about 95% water/5% acetonitrile, referred to herein as solvent A, and no more than 10% of a solvent comprising about 95% acetonitrile/5% water, referred to herein as solvent B, is injected into an HPLC instrument having a diode array uv/vis detector with a graphic display, the HPLC instrument further comprising a reverse-phase column; and eluting the material through the HPLC column using a solvent gradient profile as follows: 10% solvent B for about the first 20 minutes from start of elution, 10 to 100% solvent B gradient for about minutes 20 to 30 from start of elution, and 100 to 10% solvent B gradient for about minutes 30 to 32 from start of elution, while observing the uv/vis detector graphic display during the elution gradient over time, and separating fractions of the eluate at elution times corresponding to times associated with the graphic display peaks.

43. (Currently amended) The composition of claim 41, wherein; the reverse-phase column has dimensions of about 2.2cm X 25cm and contain about 95ml of C18 reverse phase resin, wherein the aqueous solution of the dried material from step (c) is a solution of about 50 mg of the dried material of step (c) in about 1-2 ml of solvent A, wherein the step of injecting the solution of dried material into the HPLC may be repeated, wherein a HPLC column solution gradient flow rate is set to about 5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions G though N of the eluate are collected

at the following times: fraction G (13-14 minutes), fraction H (17-20 minutes), fraction I (21 minutes), fraction K<sub>1</sub> (24 minutes), fraction K<sub>2</sub> (25 minutes), fraction L (26-27 minutes), fraction M (27-28 minutes), and fraction N (28-29 minutes).

44. (Currently amended) The composition of claim 41, wherein; the reverse-phase column with dimensions of 1.0 cm X 25.0 cm containing 20ml of C18 reverse phase resin, wherein the aqueous solution of the dried material of step (c) is a solution of 50 µg of the dried material of step (c) in 50-100µl of solvent A, wherein the step of injecting the solution into the HPLC is repeated multiple times, wherein a HPLC column solution gradient flow rate is set to about 1.5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions G through O of the eluate are collected at the following times: fraction G (12-13 minutes), fraction H (15 minutes), fraction I (16 minutes), fraction K<sub>1</sub> (20 minutes), fraction K<sub>2</sub> (21 minutes), fraction L (21-23 minutes), fraction M (23 minutes), fraction N (24 minutes), and fraction O (26-27 minutes).

45. (Currently amended) The composition of claim 19, wherein; a solution of 1 gram of the dried material of step (c) in 5 - 10 ml of solvent A is injected into an HPLC instrument having a Varian model 320 uv/vis detector set at 230 nm with a graphic display, the HPLC further comprising a 4.14 cm X 25 cm Varian Dynamax column further comprising 380 ml of C-18 reverse phase resin, the column fitted to a Varian Prostar 215 solvent delivery system; and eluting the HPLC column at a solution gradient flow rate of about 50 ml/minute, and further wherein the solvent gradient profile is with a solvent C/solvent D gradient as follows: 0-4 minutes, 25% D; 4-11 minutes, 25-30% D gradient; 11-14 minutes, 30-90% D gradient; 14-17 minutes, 90% D; and 17-19 minutes, 90-25% D gradient, where C is water and D is methanol, such that fractions of the eluate are separated at elution times corresponding to times associated with the graphic display peaks.

46. (Currently amended) The composition of claim 40, wherein; a solution of 1 gram of the dried material eluted from the second column in 5 - 10 ml of solvent A is injected into an HPLC instrument having a Varian model 320 uv/vis detector set at 230 nm with a graphic display, the HPLC further comprising a 4.14 cm X 25 cm Varian Dynamax column further comprising 380 ml

of C-18 reverse phase resin, the column fitted to a Varian Prostar 215 solvent delivery system; and eluting the HPLC column at a solution gradient flow rate of about 50 ml/minute, and further wherein the solvent gradient profile is with a solvent C/solvent D gradient as follows: 0-4 minutes, 25% D; 4-11 minutes, 25-30% D gradient; 11-14 minutes, 30-90% D gradient; 14-17 minutes, 90% D; and 17-19 minutes, 90-25% D gradient, where C is water and D is methanol, such that fractions of the eluate are separated at elution times corresponding to times associated with the graphic display peaks.

47. (Currently amended) The composition of claim 42, wherein; the reverse-phase column has dimensions of about 2.2cm X 25cm and contain about 95ml of C18 reverse phase resin, wherein the aqueous solution of the dried material of step (c) is a solution of about 50 mg of the dried material of step (c) in about 1-2 ml of solvent A, wherein the step of injecting the solution of dried material into the HPLC may be repeated, wherein a HPLC column solution gradient flow rate is set to about 5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions G though N of the eluate are collected at the following times: fraction G (13-14 minutes), fraction H (17-20 minutes), fraction I (21 minutes), fraction K<sub>1</sub> (24 minutes), fraction K<sub>2</sub> (25 minutes), fraction L (26-27 minutes), fraction M (27-28 minutes), and fraction N (28-29 minutes).

48. (Currently amended) The composition of claim 42, wherein; the reverse-phase column with dimensions of 1.0 cm X 25.0 cm containing 20ml of C18 reverse phase resin, wherein the aqueous solution of the dried material of step (c) is a solution of 50 µg of the dried material in 50-100µl of solvent A, wherein the step of injecting the solution into the HPLC is repeated multiple times, wherein a HPLC column solution gradient flow rate is set to about 1.5 mls per minute, and further wherein the solvent gradient profile is 10% solvent B for 0 to 20 minutes, followed by 10 to 100% solvent B gradient for minutes 20 to 30, and 100% to 10% solvent B gradient from minutes 30 to 31; such that fractions G though O of the eluate are collected at the following times: fraction G (12-13 minutes), fraction H (15 minutes), fraction I (16 minutes), fraction K<sub>1</sub> (20 minutes), fraction K<sub>2</sub> (21

minutes), fraction L (21-23 minutes), fraction M (23 minutes), fraction N (24 minutes), and fraction O (26-27 minutes).

49. (Currently amended) An Uncaria extract composition made according to a method comprising the step of:

- a) preparing a polar solvent extract of *Uncaria* plant matter,
- b) running the extract through a first column that comprises hydroxy group containing resin, resin having hydrophobic characteristics but without any hydroxy groups, or a mixture of both,
- c) washing the first column first with distilled water, then with a dilute polar alcohol/water solution,
- d) eluting the first column with a polar alcohol/water solution, and lyophilizing the eluate,
- e) applying an aqueous solution of the lyophilized eluate of step (d) to a second column,
- f) eluting the second column with successive column volumes of water/methanol mixtures containing 0.1% TFA, beginning with 25% methanol and increasing to 100% methanol in 25% increments,
- g) collecting, combining and lyophilizing the eluate,
- h) HPLC purifying a solution of the lyophilized eluate of step (g) prepared in a solvent comprising about 80% water/20% methanol and about 0.1% TFA and applied at about 150 mg/run with detection at 280 and 300 nm, gradient conditions being 0 to 3 min for 20% to 25% methanol and about 0.1% TFA, 3 to 9 min for 25 to 45% methanol and about 0.1% TFA, all at a flow rate of about 20 ml/min, and
- i) collecting a fraction eluting between 7-8 minutes from start of the HPLC purification.